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Concerning Recurrent Transient Cerebral Ischemic Attacks

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ONE of the commonest problems in the practice of medicine is the interpretation of transitory spells or attacks of central nervous system origin. Epilepsy, syncope, vertigo and migrainous aura, to mention the more important, have been well described clinically and investigated thoroughly during the past several decades. Another class of evanescent episode, although of equally ancient origin and recognition, has been fully delineated only comparatively recently, and here I refer to the transient attacks of cerebral ischemia associated with arterial atherosclerosis and thrombosis. While these brief spells of numbness, paralysis, dizziness, and so forth are often the forerunners of neurologic disaster, "straws which show how the intracranial wind is blowing", they not uncommonly prove benign and cease without any major sequelae. At present their clinical importance lies in the opportunity they provide us as physicians to introduce therapeutic measures before the full thrombotic stroke occurs, for it is a fundamental fact that the only treatment of a stroke due to ischemic infarction is the prevention of it. Once the cerebral tissues have been wrecked, every effort will avail nothing. It must be admitted that preventive measures—anticoagulants, surgical endarterectomy of cervical arteries, cessation of smoking, dietary restriction, avoidance of hypotension, etc.—have not yet been shown to be beneficial by means of scientifically designed therapeutic tests, but much of the available evidence hints that they are of some value in properly selected cases.

In the light of the currently revived interest in cerebrovascular disease, I propose to review and discuss a few aspects of transient ischemic attacks of cerebral origin.

At the outset some limits must be placed on the word "transient", and we might arbitrarily reserve this term for episodes lasting less than 24 hours. Cases of transient ischemic attacks (TIA) may be divided roughly into three types: (1) those in which only a single episode occurs, (2) those with multiple attacks of approximately the same pattern, and (3) those with multiple attacks of different patterns. It is the second type which will be discussed in this report, namely recurrent spells of the same pattern, a subject which has a rather brief history in the medical literature. In the past there have been not infrequent references to transient hemiplegia or amaurosis in which the neurologic deficit of a *single* brief stroke cleared completely in a period of hours up to several days, but these single episodes are to be sharply distinguished from *recurrent multiple* TIA. Recurrent attacks are usually the result of atherosclerosis and thrombosis, and reflect repeated transient local ischemia which is reversed or corrected before irreparable damage to tissue occurs. The attacks are all similar with only minor variations, and usually they are more evanescent than the single-episode type. Such attacks of the same pattern are never caused by hemorrhage or by an established infarct; neither ordinarily will cerebral embolism be responsible, since embolic particles arising in the heart, for example, would hardly enter the same distal arterial branch repeatedly. Single spells (Type 1), which clear in a short time, may result from embolism, from thrombosis causing a small infarct (a lacunar infarct), or even from a small hemorrhage, although even the smallest hemorrhages take at least several days to clear. Or the single episode may be the first in a series of TIA which will make their appearance in the not-too-distant future. Multiple evanescent strokes of different pattern (Type 3) may be caused by multiple episodes of embolism, small infarction or hemorrhage of restricted size.

Recurrent TIA preceding a stroke are rarely mentioned in the literature. They were described in one case by Peabody in 1891,[1] but surprisingly no brain lesion was found at autopsy. It might be interjected here that, while the pathologist might not find a blocked artery at autopsy, it is almost unheard of not to find a brain lesion in the presence of a major stroke. Russell[2] in 1909 described a

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patient with approximately a dozen attacks of hemiplegia in eight months, but the patient was then lost to follow-up. On the occasion of this meeting of The Canadian Medical Association it is especially appropriate to note that Sir William Osler[3] reported how, as a young man in Montreal, he had the unhappy experience of calling upon his friend Dr. George Ross to find that Dr. Ross had just experienced an alarming spell of paralysis. It was to be the first of many transient attacks of aphasia, monoplegia and hemiplegia extending over a period of four or five years. Osler favoured vasospasm as the explanation of these attacks. His report was made in 1911 in Volume 1 of the newly founded *Canadian Medical Association Journal* which is celebrating its semi-centennial year of publication.

After 1911, very few papers dealt with recurrent TIA until the advent of our recent knowledge of thrombosis of the carotid arteries.[4] In 1950, at the Neurology Clinic of Queen Mary Veterans Hospital, Montreal, an unfortunate victim of hemiplegia, as he mournfully related his tale of misery, mentioned how in the weeks before his stroke developed, he had several times become temporarily blind in one eye. While the note in the record was being completed, he remarked, "Isn't it funny that I went blind in the wrong eye? My paralysis is on the left and it was my right eye that went blind." The significance of this history, although readily apparent today, was not recognized at that time. One week later another patient presented with an almost identical history. He stated that prior to his stroke he had several times noted transient blindness in one eye while imbibing at his local tavern. Upon telling his friends of this they said "Don't worry, everybody has those things. It will be all right in a minute," and it was. The coincidence of the histories of these two patients prompted some reflection as to the mechanism of the stroke, and the possibility of internal carotid artery disease came to mind. A few days later, direct questioning of another stroke patient revealed a third instance of premonitory transient monocular blindness. Gathering proof that carotid occlusion was actually responsible was another matter. However, the first patient just referred to was discovered to have widespread carcinomatosis and had but a short time to live. It happened that he died one weekend while I was away from the city, and on returning late Sunday evening I learned that, although an autopsy had been performed, the carotid arteries in the neck had not been examined. The burial was scheduled for the following day. With more than a little hesitation and reservation I determined to see if anything could be done regarding the carotid arteries. A telephone call to the grieving widow brought a surprisingly prompt acquiescence, and there remained only arrangements with the funeral director. Here again understanding and co-operation beyond belief were displayed, and midnight witnessed the belated removal of the carotid arteries from the neck. The excitement with which I incised the region of the carotid sinus on the right side and found total occlusion of the lumen can well be appreciated. It was one of the first cases, if not the first case, of clinically diagnosed internal carotid artery thrombosis to be confirmed at autopsy and the premonitory phenomena had provided the clue to the diagnosis. It might be added parenthetically that I also remember the words of the funeral director, who unfortunately must go unnamed, when I apologized in the early morning hours for disturbing his handiwork. His reply was to the effect that I was to think nothing of it, and if he could not mend the imperfections left by the pathologist, he ought not to be in the business.

Soon thereafter the idea was entertained that by taking advantage of the premonitory symptoms in stroke cases one might be able to introduce prophylactic measures, especially anticoagulants, before the full paralysis had been precipitated. With this in mind, each stroke patient at the Montreal General Hospital, Queen Mary Veterans Hospital and St. Anne's Hospital, Montreal, was questioned regarding the occurrence of prodromal symptoms. It was truly remarkable to find a history of such episodes in case after case, and in some an incredible story was obtained of repeated spells numbering in the hundreds, extending over days, weeks or months. They seemed to occur with strokes in every arterial territory, and TIA were recognized in the carotid, basilar, vertebral and posterior cerebral regions.[5] Although all of this is now commonplace knowledge, it is not long since that patients with vascular syndromes which are easily recognized today were still being subjected to pneumoencephalography in search of a brain tumour. The realization that prodromal phenomena were so frequent led in turn to the use of anticoagulants as a prophylactic measure in cases of cerebral thrombosis. Surgical correction of the carotid obstruction was also suggested at that time,[6] as the result of a conversation at the luncheon table at the old Montreal General Hospital with the late Dr. R. R. Fitzgerald.

THE CLINICAL PICTURE IN TIA

Recurrent TIA vary in duration from case to case and in the same case from one attack to the next. The briefest last but a few seconds, the longest may take several hours to clear. A duration of from one to 10 minutes is common. There may be only one attack preceding the stroke, and it may occur days or weeks before; or hundreds of spells over a period of days, weeks or months may antedate the stroke; or a flurry of episodes may come and go without a stroke ensuing. So far it has not been possible to predict which patients will fare well and which will develop a stroke. The neurologic features of the attack depend on the artery involved and are but fragments borrowed from the impending stroke. It would appear that TIA occur with thrombosis of all cerebral arteries, large and small.

In the carotid—middle-cerebral territory the commonest symptoms are weakness, paralysis, numbness, tingling or heaviness, involving the opposite limbs or opposite side of the face. Motor symptoms are much more frequent than sensory and occur in seven out of 10 cases. Most commonly, the face, arm and leg are affected together; next in frequency come the arm alone, leg alone, face and arm, and arm and leg in that order. Ipsilateral transient monocular blindness occurs in 40% of symptomatic carotid cases. Other visual symptoms are uncommon in patients with carotid artery disease. It is my impression that visual scintillations, as occur in a migrainous aura, never arise in patients with thrombosis in the middle cerebral artery territory, only in those with posterior cerebral involvement. Aphasia may be the only symptom in carotid artery disease involving the dominant hemisphere, but usually it occurs in combination with other symptoms. Transient attacks of confusion are infrequent, and an accurate history usually discloses that aphasia is the basis of the confused state. In slight spells the patient may speak only of veering to one side while walking. A frank focal convulsive seizure with jerking is a great rarity, but the patient may speak of the affected parts as trembling, shaking, twisting, drawing up or moving irregularly. This distinction from epilepsy may seem to be hair-splitting, but I believe that the movements associated with TIA are not really convulsive in nature, and indeed similar movements are seen in patients with basilar artery lesions where the disturbance is remote from the cortex. The movements never go on to a generalized seizure, and a generalized seizure with unconsciousness must not be construed as evidence of a TIA.

In the vertebral-basilar territory the symptomatology of TIA is much more diverse, since so many different neural structures are involved. Analysis of our data showed that the commonest symptom by far was dizziness, either alone or more usually in combination with other symptoms. Dizziness occurred in no less than three-quarters of all cases. The symptoms associated with dizziness included, in order of frequency: diplopia, dysarthria, hemiplegia or hemiparesis, numbness, dysphagia and headache. In the absence of dizziness, unsteady gait and dim vision were the two predominant symptoms. Since dizziness is rare in patients with internal-carotid—middle-cerebral lesions, it can be regarded as the tell-tale sign of basilar artery involvement. Diplopia is another reliable sign of brain-stem involvement. Mental confusion which occurs infrequently is characterized by transient loss of memory and in the light of recent neurophysiological discoveries probably reflects involvement of the hippocampal region. One of our patients had brief spells in which he did not know where he was, yet was perfectly intact otherwise. Finally in one of the attacks he developed weakness in all limbs, and dysarthria, and proved to have basilar artery occlusion. Thus confusion in internal carotid disease connotes aphasia in many cases, whereas in vertebral-basilar disease it means memory loss. This points up the fact that we as clinicians must always try to dissect and characterize confusional states and not be satisfied with merely using the rather chaotic term, "confusion". Attacks of quadriplegia or quadriparesis, which are a hallmark of vertebral-basilar disease, do not occur as isolated phenomena, and there will always be other evidences of brain-stem involvement such as dizziness or diplopia in such cases. Headache may occur in association with TIA, but more commonly it occurs later during the period of progressive evolution of the persistent stroke. Focal convulsions have not been recorded but, again, irregular tremblings or movements of the limbs, as previously mentioned in the discussion of internal-carotid—middle-cerebral artery attacks, may be noted. Generalized convulsions have not been encountered. It might be emphasized here that loss of consciousness is rarely a manifestation of TIA, but occasionally a patient with total paralysis will be unconscious also. Syncope is rarely if ever seen, but in basilar TIA, pallor and sweating are often remarked upon. In the syndrome of the "subclavian steal", described below, a feeling of faintness is frequent.

As an example of an unusual case, I might mention a patient with basilar artery occlusion whose initial attack consisted of falling into what appeared to be a sound sleep just prior to which the right eye elevated to the 11 o'clock position and the left eye to the 1 o'clock position. After 10-15 minutes he became wide awake and went on with his business. The attacks were wrongly interpreted as insulin reactions. Dr. Francis McNaughton has told me of a patient who had brief episodes of hemiballismus preceding his stroke. Another patient experienced episodes of peduncular hallucinosis in which he episodically had vivid visual hallucinations of life-like Lilliputian figures.

This has been a rather brief review of the clinical features of TIA, and a wealth of the most interesting neurologic events lies buried in these generalizations and broad statements.

THE PATHOLOGICAL BASIS AND PATHOGENESIS OF THE ATTACKS

Linked to an oncoming thrombotic stroke as these recurrent transient episodes so often are, it is almost axiomatic that firstly they are ischemic in nature rather than convulsive and secondly they are caused by the same factors which sooner or later will determine permanent failure of the local circulation. The arterial lesion in a great many instances is atherosclerosis and superimposed thrombus resulting in stenosis of the lumen. DeBakey[7] found by arteriography in 146 cases in which TIA were caused by lesions of the extracranial carotid and vertebral arteries (carotid 88, vertebral-basilar 58) arterial stenosis in 92, complete occlusion in five and a combination of stenosis

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of one vessel and occlusion of another in 49. Therefore, according to DeBakey, if the responsible arterial lesion (or lesions) is extracranial, a stenotic vessel is the anatomical substrate of TIA in 96% of cases, either alone or in association with occlusion of another major vessel. It probably is safe to extend these findings to the intracranial vessels. Judging from our pathologic observations of the great frequency of cerebral arterial stenosis without symptoms, arterial narrowing must be severe before TIA occur, the diameter of the arterial lumen probably being reduced by at least 80%. Even then, symptoms by no means always occur, for asymptomatic occlusion of one internal carotid artery is not uncommon. In studying this matter, postmortem examination is not very helpful, since rarely does the patient die from another cause during the period in which he is experiencing TIA. Usually many months will have passed during which the thrombus will have changed and a stroke may have supervened. However, some of our autopsy studies in cases in which a rapidly fatal stroke followed upon a long period of TIA have shown a greatly narrowed arterial lumen blocked by a recent clot. The narrowing of the lumen has been due to atherosclerosis and superimposed layers of organizing thrombus of different ages, this gradual stenosis probably determining the occurrence of the preceding TIA. A careful pathological study of the unmutilated carotid endarterectomy specimens removed in cases of TIA would be most informative.

Nonetheless, cases of TIA occur in which the main artery is certainly totally occluded at the time of symptoms, and here it must be assumed that the *collateral* circulation fails temporarily, possibly in association with stenosis of a major collateral channel, e.g. the opposite carotid artery or the external carotid. Stenosis of collaterals may be an unnecessary assumption, and it may well turn out that, in a multi-channelled system such as the cerebral arterial tree, collateral flow might fail intermittently because the anastomotic vessel in its normal condition constitutes a channel of borderline adequacy.

For purposes of discussion one might conveniently divide these cases into two groups—"simple" or "non-anastomotic", in which the stenotic artery furnishes the entire blood supply of its territory between attacks, and "anastomotic" cases, in which the territory of the stenotic (or occluded) artery is dependent, wholly or in part, on collateral flow between attacks. It is well to remember that a compromised territory may receive its blood supply *jointly* from one, two or even three collateral or anastomotic sources, each contributing its different share of the whole supply and having a corresponding potential for evoking ischemia if its contribution fails.

With this knowledge of the pathologic substrate, let us now look further into the mechanism of the attacks, in particular the *intermittence* of symptoms. It should be pointed out immediately that *intermittence* can be recognized not only in the period of TIA but during the entire thrombotic process, including the period of the persistent stroke which so often develops in a stuttering, step-wise fashion, with fluctuations from hour to hour or day to day, rather than gradually and evenly. All stages of thrombotic infarction must be examined for clues. For years vasospasm has been a favourite explanation but one for which there is no direct evidence. For those who would disclaim the occurrence of cerebrospasm, the current theory of migrainous auras which attributes them to arterial constriction is a mental hurdle. Some 40 years ago in connection with *single* transient strokes, objections to vasospasm as a mechanism were raised and it was suggested that a drop in the systemic blood pressure in the elderly and arteriosclerotic individual, as occurs on arising in the morning, after eating, postoperatively, or with myocardial infarction or anemia, precipitated cerebral ischemia which was relieved as the systemic pressure was elevated again.[8] Pickering,[9] arguing from the evanescence of some embolic episodes, suggested that the single temporary strokes of patients with severe essential hypertension might be due to vascular occlusion rather than to vasospasm. Denny-Brown[10] rejected vasospasm as the cause of TIA and favoured transient fluctuations in the systemic blood pressure compromising a precarious cerebral blood supply.

In recent years much additional information has accumulated concerning TIA. First of all there is fairly good evidence that anticoagulants such as heparin (and/or dicoumarol) reduce the frequency of attacks. In a randomized series of patients with TIA treated with and without anticoagulants the group receiving anticoagulants experienced only 20 attacks in all, and the control group 570 attacks, confirming the conclusions of our earlier studies at the Montreal General Hospital.[11] Thus it would appear that the thrombotic process within the arterial lumen plays some role in determining the occurrence of TIA, and one might surmise that this applies to those cases in which arteriography shows stenosis as the only abnormality. This would also be consistent with our pathologic findings mentioned above. Embolic clot, on the other hand, rarely produces transient attacks and never a large number, probably because the lumen rapidly becomes totally occluded. It is to be emphasized, however, that heparin does not abolish attacks in all patients with TIA. Also it is possible that anticoagulants might affect blood flow via an anti-sludging action or change in viscosity rather than by a direct influence on the thrombus. Supporting this latter proposition is our finding that in cases of basilar artery occlusion, when the lumen is totally obstructed by *atherosclerosis* and collateral flow becomes all-important, anticoagulants transform a stuttering stroke into a smoothly progressive one

simulating the picture produced by a rapidly growing glioma.

In regard to the role of posture and hypotension in TIA, review of our data shows that the overwhelming majority of TIA occur when the patient is up and around rather than lying horizontal. They occur not infrequently in the morning shortly after arising or in relation to breakfast. In many instances they have occurred on standing up and were relieved by lying down, or they occurred after a hot bath or while taking antihypertensive blocking agents. The following illustrative case is a rather striking example of the effect of posture. A 57-year-old previously healthy woman jumped up from a couch on which she was lying in order to answer the telephone. She collapsed to the floor but was able to crawl to the next room and reach up to a table to take the telephone. On attempting to talk an unrecognizable jumble of words came out although she knew what she wanted to say. Within 20 minutes she had returned to normal but her physician nonetheless sent her to a hospital emergency ward where a diagnosis of hysteria was made and the patient was sent home. Her physician sent her back for further investigation, and arteriography showed bilateral, complete occlusion of the internal carotid arteries. Blood reached the right hemisphere via collateral flow through the right external carotid artery and ophthalmic artery and the left cerebral hemisphere was supplied from the basilar artery via the posterior communicating artery.

Postural hypotension must always be sought in cases of TIA. We have recently examined two patients with many TIA who proved to have postural hypotension associated with hypothyroidism. Thyroxin and elastic supports were beneficial. In another patient who developed a brief stroke on straightening up after bending down behind the counter in his store, the blood pressure on standing up immediately fell precipitously to 60 mm. Hg systolic, recovering satisfactorily in the next few minutes. Such a brief flash of postural hypotension could be easily overlooked.

These observations point to the possibility that a temporary decrease of blood flow to the cerebrum associated with the upright position is an important pathogenetic factor. Yet tilting such patients on a tilt-table and lowering the blood pressure to almost syncopal levels has usually failed to precipitate an attack.[12] However, tilting is such an abnormal procedure that perhaps we should not expect it to mimic everyday activity. Also many patients subject to TIA have suffered catastrophic falls in blood pressure as a result of hemorrhage, myocardial infarction and so forth without suffering a stroke. TIA may certainly occur while the patient is reclining, and I personally have observed numerous attacks come and go while the patient lay quietly without changing his position and while the blood pressure did not fluctuate appreciably. Furthermore, one patient may have attacks under varied circumstances, e.g. shortly after arising, later in the day, standing, sitting or even reclining. It is rather uncommon for a TIA to be present when the patient awakens in the morning. This poses a conundrum, for in our cases of cerebral thrombosis the stroke has developed during sleep in 57% of cases and within an hour of arising in another 25% of cases. Thus, strokes tend to occur while the patient is lying asleep whereas TIA are related to being awake, up and around. The reduced cerebral circulation of sleep seems to outweigh the advantage of the horizontal position and converts a TIA into a persistent stroke. It is my experience that awakening with a neurologic deficit, albeit a transient one, is a serious omen.

Transient attacks have been related to exercise, exertion, sneezing, coughing, outbursts of temper, smoking or laughing. One of our patients with bilateral carotid occlusion developed bilateral blindness while running to put another coin in a parking meter. In the same patient blindness had occurred during violent arguments. Dr. Joseph Pritchard of the Montreal General Hospital has acquainted me with the case of a 70-year-old hypertensive butcher who had several transient episodes of right hemiplegia and aphasia associated with outbursts of temper, usually directed at his customers. Paralysis which was severe often came on suddenly, and on more than one occasion the meat cleaver had flown from his hand. Recovery usually began in a few hours and was complete in 12 hours, paralysis usually passing off during his sleep. On one occasion on passing the butcher shop and hearing the patient involved in a violent quarrel with a customer, Dr. Pritchard was moved to remark that he would soon be hearing from the butcher's family. Within a few minutes of reaching home a message came saying that the patient had just fallen into one of his typical attacks.

A recent finding in TIA is that cases in which numerous episodes occurred over a long period of time (weeks or months) usually proved to have large vessel disease affecting the carotid, vertebral, basilar, middle, anterior and posterior cerebral arteries. In those with thrombosis of smaller vessels, e.g. the penetrating branches, central retinal artery and branches of the basilar and vertebral arteries, prodromal phenomena were less numerous and the period of their occurrence was much briefer, often hours or days. This was true also in the lateral medullary syndrome which is usually caused by vertebral artery thrombosis[13] blocking the mouths of small arterial branches supplying the lateral medulla. However, the premonitory spells need not be numerous in patients with thrombosis of the larger vessels, and indeed there may be only one or two such spells. The occurrence of numerous TIA in patients with disease of the large arteries of the circle of Willis, and their relative infrequency in those with disease of the penetrating vessels which lack anastomotic connections, might suggest that collateral flow intervenes and prevents the

transformation of transient ischemia into infarction. The availability of collateral circulation would accordingly be the chief factor in extending the signs of cerebral thrombotic occlusion over a period of days, weeks and months. Another possibility is that in a small vessel a critically stenosed lumen might become irreversibly totally occluded more readily than in a large artery where the residual lumen is greater, with the result that in the former the stroke would evolve over a relatively short period.

Transient ischemic attacks have been ascribed to intermittent compression of the vertebral arteries upon rotation of the neck, but rarely are such cases convincing. I have not seen a good example of this occurrence personally, nor have several of my colleagues. Further studies of this matter are in order. Kinking of a redundant carotid artery in the neck has also been implicated.

Analysis of our cases shows, surprisingly, that TIA rarely occur in the presence of atrial fibrillation, and in the past year not a single case of this nature has been encountered.[12] This matter also deserves further study.

A newly described condition which we have termed the "syndrome of the subclavian steal" is of considerable interest. Atherosclerotic occlusion or stenosis of one subclavian artery proximal to the origin of the vertebral artery results in retrograde flow down the corresponding vertebral artery to supply the arm, draining blood away from the basilar system with the production of brain-stem ischemia. The commonest symptoms in such cases are dizziness, indistinct vision, unsteady gait and faintness. During the attacks there may be a throbbing or beating in the suboccipital region on the affected side associated with aching or pain in the same region. Attacks of numbness and paralysis of various parts of the body are not infrequent. Toole[14] described a case in which symptoms were brought on by exercising the corresponding arm and relieved by resting. Rob[15] cured such a patient by actually ligating the run-off vertebral artery in the neck, in this way preventing diversion of blood from the basilar system. I have notes on 33 patients examined in the last 10 years in whom there was reduced blood pressure in one or both arms (right 7, left 21, bilateral 5). Although these cases were highly selected in that they were examined because of manifestations of cerebrovascular disease, it is of interest that no less than 23 had symptoms which conceivably could be attributed to the presence of a "subclavian steal". The left arm was affected more than twice as frequently as the right, probably because the left subclavian artery arises directly from the aortic arch and is subject therefore to greater atherosclerotic propensity. Cases with bilateral reflux may be expected to occur, and also cases in which the contralateral vertebral artery is vestigial or previously occluded, the retrograde blood flow then coming from the carotid system via the circle of Willis. In some cases of the aortic-arch syndrome the symptoms reflect the presence of a "subclavian steal" as we have witnessed in a patient with Takayashu's disease. Thus careful assessment of the pulses and blood pressure in the upper extremities is in order in all patients with cerebrovascular disease. The occurrence of transient episodes of all kinds in association with the "subclavian steal" demands that these patients be carefully examined for any light that they may shed on the pathogenesis of transient ischemia. Major shifts in the pattern of cerebral blood flow during sleep and exercise, and with changes in posture, would seem to be incriminated.

It might be imagined that examination of the eyegrounds during an episode of transient monocular blindness might throw light on the whole phenomenon of intermittence of the manifestations of TIA. We have previously reported[16] a patient who had had several hundred attacks of blindness in the left eye in addition to episodes of numbness and weakness of the right side over a period of one and a half years. Carotid arteriograms showed stenosis in the region of the carotid sinus. Observation of the fundus during attacks of blindness was possible on two occasions, and an unusual picture was witnessed. At the height of the blindness a brilliantly white mass blocked the central artery at the optic disc, and over the next 40 minutes the mass migrated distally along the superior temporal artery, being temporarily arrested at arterial bifurcations. The nature of the material was not known, but a platelet mass or some sort of coagulum was suggested. That TIA might be related to the passage along the artery of some material was a rather unexpected finding, yet this identical process was seen on two different occasions. After dicoumarol therapy was started no further episodes occurred. An idea of the arterial pressure changes in TIA is obtained in cases of transient monocular blindness in which the pressure in the central retinal artery usually is 40-60 mm. Hg between attacks.

It is known that embolic particles break off from the sites of thrombus formation in the carotid, vertebral and basilar arteries[13] (we have called this "local embolism"), but just as in the case of emboli arising in the heart, such fragments would hardly lodge in the same distant branch repeatedly to cause recurrent TIA of the same or approximately the same pattern. It should be re-emphasized that recurrent attacks in any one patient tend to be of the same general nature, although varying in extent of involvement as well as in duration and pattern. Embolism would be an unlikely explanation in cases where TIA occur every few minutes for two or more hours. A major embolic occlusion of the internal carotid artery may be associated with transient monocular blindness in the period immediately after onset, and to support the "local embolism" theory of TIA one would have to postulate that daughter emboli break away to enter the ophthalmic artery. Also in cases of thrombosis of

the basilar artery local embolism would not account for episodes of total quadriparesis with preservation of consciousness, for an embolus would not at any time, let alone repeatedly, lodge in the mid-basilar artery which is what it would have to do to spare the mid-brain and consciousness.

Millikan *et al.*[17] have reported TIA in cases of polycythemia, the attacks ceasing as the patient's hematocrit returned to normal, suggesting that blood viscosity was a factor. This would still not account for the intermittence of symptoms. The relation of TIA to the ingestion of food has not been determined as yet, but in view of the effect of ingestion of fat on the physical properties of the blood this might well be worthy of investigation. I have encountered cases in which giving up cigarette smoking has led to prompt cessation of TIA, and conversely, cases in which abstinence from alcohol has been associated with their appearance. A systematic trial of the effect of carbon dioxide inhalation on the duration of TIA has never been undertaken and might throw some light on the mechanism of their production.

Concerning the change in the process going on within the arterial lumen as TIA's give way to a persistent stroke, Crawford[18] has reported that in patients with carotid involvement, operated upon during the progressive evolution of a persisting thrombotic stroke, the most frequent finding was stenosis of the vessel with a superimposed "rat-tail" blood clot extending upwards to block the lumen above. In other words, TIA's, at least in some cases, lose their transiency with the advance of the thrombotic process.

The foregoing by no means exhausts all of the observations which might be considered in theorizing about TIA. For example, recent studies[11] indicate that not infrequently TIA's cease without a stroke ensuing. This has not been explained so far, but one might conclude that TIA's are less likely to occur after total occlusion of a vessel when a stable abundant collateral flow has been established —sufficient to prevent infarction—than in the presence of stenosis with its tendency to instability and change. Another possible explanation would be that gradual establishment of adequate collateral flow alone has taken place, although it must be admitted that the change of collateral flow with time remains totally undocumented so far as the cerebral circulation is concerned. Equally puzzling are the cases of carotid stenosis with TIA in which the internal and external carotid arteries can be clamped indefinitely during surgical procedures without precipitating cerebral symptoms.

In patients with carotid disease, transient attacks of monocular blindness and attacks of weakness and numbness may both occur, but rarely do they occur at the same time. In those with basilar disease a right hemiplegia may occur on one occasion, a left hemiplegia the next. What determines this seemingly haphazard pattern? *Local vascular factors* must determine the distribution of the limited amount of blood passing the region of stenosis or flowing in via collateral channels. In this regard the cerebral arteries are by no means inert tubes, but rather are they capable of important *auto-regulatory* changes. For example, in patients with hypertension the cerebral blood flow is not increased, since the cerebral arteries constrict in response to the rise in pressure. Also when one internal carotid artery is ligated the total cerebral blood flow may not be much altered, for the arterial tree on the side of the ligature relaxes and reduces the peripheral resistance, encouraging adequate flow at a lower pressure. Carbon dioxide inhalation increases cerebral blood flow by up to 50%. Distal to a stenosis the arteries are no doubt subject to similar intrinsic changes, but being unmeasurable, it is impossible to decipher the exact alterations in the patterns of blood flow.

In cases with prodromal transient monocular blindness only very rarely is vision affected at the time of the stroke, and after the stroke, even one of mild degree, the attacks of blindness usually cease. Again it seems that collateral flow cannot adjust sufficiently quickly to intermittent dynamic changes in the territory of a stenotic artery, but when occlusion occurs and obligatory collateral flow becomes permanently established, it proves to be both adequate and stable. In one rather remarkable case of total occlusion of the internal carotid artery with some 35 attacks of weakness of the opposite arm, arteriography showed filling of the intracranial arteries via the external carotid and ophthalmic arteries. At operation, which failed to reopen the internal carotid artery, temporarily clamping the external carotid artery evoked an attack. Postoperatively the external carotid artery became occluded by thrombus, but there were no ill effects and transient spells ceased thereafter.

When transient monocular blindness occurs in the course of internal carotid artery thrombosis, it is one of the earliest manifestations and is not added as a late development. The so-called vasospasm (or narrowing of the lumen) seen in intracranial vessels in patients with ruptured aneurysm does not cause TIA. Hyperventilation, which constricts cerebral vessels, has never in our experience precipitated a transient attack. Surgical ligation of the common carotid artery, as practised in the treatment of ruptured saccular aneurysm, almost never leads to multiple TIA of either transient monocular blindness or weakness. A finding of some interest is that in patients with arteritis, e.g. temporal arteritis or syphilitic arteritis, transient spells are almost unknown, suggesting that the thrombus associated with inflammation is formed in such a way or at such a tempo that transiency tends to be excluded; or possibly it is because the arteries involved are small.

With all of this information at hand, can a satisfactory explanation of the intermittence of symptoms be formulated? It would appear to us that there is more than one mechanism. First of all,

attacks may be caused by the passage of an embolic platelet mass or coagulum as observed in the retinal artery in the patient previously described. It would be helpful to know if the events witnessed in the retinal vessels actually represent what occurs in those of the central nervous system.

When embolism is not operative and stenosis of the lumen is the basic substrate of the attack, ischemia is precipitated by (a) decreased flow along the main feeding artery, (b) an increase in the size of the thrombus, or (c) a diversion of blood to one distal branch at the expense of another. These may be called *precipitating* factors. Reversal of the ischemia within a few minutes and prevention of infarction must be attributable to one or more of four *restoration* factors: (a) restoration of flow and pressure along the main artery, (b) collateral influx, (c) a decrease in the size of the thrombus, or (d) auto-regulatory changes in the distal arteries. In attacks which clearly occur in relation to postural changes or in association with postural hypotension one must implicate in the "simple" case a transient reduction in blood flow through the main artery; in the "anastomotic" cases reduction of flow would occur in the collateral channels if the main artery were occluded, or through both the direct and collateral channels if the main artery were only stenosed. Recovery occurs via any of these four restorative factors.

That TIA might be due to alterations in the size of a thrombus is largely speculative except for the fact that heparin abolishes these attacks. Possibly anticoagulants not only prevent further thrombus formation but lead to decrease of thrombus already deposited, thus aiding flow through the direct channel of supply. The general efficacy of anticoagulant therapy in TIA suggests that, during the period of their occurrence, the blood supply is in a very precarious balance.

The pattern of flow in a multi-channelled interconnecting system, such as the cerebral arterial tree, probably undergoes fluctuations apart from postural change, with the result that the adequacy of collateral flow will vary and possibly TIA will be precipitated. This type of mechanism is exemplified in the "subclavian steal" which can be related to muscular exercise of the involved arm. The role, if any, of "auto-regulation" in precipitating TIA remains unknown, but it is conceivable that under certain anatomical circumstances local vascular changes, by increasing the flow in one arterial branch, might divert essential blood from a neighbouring branch. In some cases with carotid involvement, the occurrence of TIA while eating and chewing might even suggest that blood is directed to the masticatory muscles and salivary glands at the expense of the collateral flow to the brain via the ophthalmic artery. With regard to auto-regulation and the restoration of flow in TIA, the local accumulation of carbon dioxide in an ischemic zone could well cause vasodilatation resulting in increased flow and cessation of the attack.

THE DIFFERENTIAL DIAGNOSIS

Finally I should like to comment on rules regarding the differential diagnosis and treatment of TIA which we have found to be of help. (1) Loss of consciousness is extremely rare and indicates another diagnosis—such as seizures, syncope, Stokes-Adams attacks, and so forth. (2) A generalized seizure also refutes the diagnosis of TIA. (3) A frank focal seizure is extremely rare, and if it goes on to a generalized seizure and unconsciousness the diagnosis of TIA is untenable. (4) Transient loss of memory is scarcely ever due to a TIA. A more likely diagnosis is *transient global amnesia.* More than 25 cases of this condition have now been examined in the last few years. It seems not to be ischemic in nature, but rather a seizure manifestation. It is always benign. (5) Dizziness without other accompaniments, either on history or examination, is rarely due to TIA. Our present rule is that dizziness due to ischemia will not persist for more than two weeks without providing evidence of brain-stem involvement by history or examination. Dizziness as an isolated symptom is not an indication for anticoagulant therapy. In many cases in the middle-aged and elderly, dizziness occurs in association with an acuity of hearing which is average *for that age* and with little or no tinnitus. Hearing is often pronounced as *normal* by the otologist and the dizziness ascribed erroneously to brain-stem vascular disease. I believe that these cases, which are extremely common, represent pseudo-Ménière's syndrome. One might refer to this condition as "presbyvertigo" analogous to the terms presbyopia and presbyacusis. (6) Visual scintillations or flickerings of the migrainous type without headache are not infrequent in the middle-aged and elderly. They are usually although not always benign. They are never an indication for anticoagulant therapy. (7) TIA may occur with cerebral hemorrhage or cerebral embolism, but so rarely as scarcely to deserve mention. Occasionally a single TIA is reported before a hemorrhage, but in most cases it is coincidental. However, we have had two patients who developed a sudden transient hemiplegia at the onset of their illness, in whom rupture of the vessel presumably interfered with blood flow distally. Recovery occurred in a matter of minutes and later a slow recurrence of the hemiplegia took place. An embolus lodging in the internal carotid artery may be associated with one or even a few TIA in a period of not more than 24 hours before the stroke persists. (8) Brain tumours may occasionally cause transient symptoms, possibly by pressing on a nearby artery. I have encountered three such striking cases with a tumour in the anterior cerebral territory causing transient attacks of weakness of the corresponding leg over a period of several weeks. (9) The diagnosis of carotid stenosis or occlusion can be made on clinical grounds in nine cases out of 10 from the following criteria: (a) a history of transient monocular blindness; (b) absence of pulsation in the common carotid or internal carotid

or external carotid artery; (c) a bruit over the ipsilateral carotid sinus or the contralateral orbit; (d) unilateral or bilateral reduction of the central retinal artery pressure. An arteriogram should only be confirmatory. If the patient is unable to cooperate or if no history is available, this is another matter.

Our need to interpret TIA correctly is constantly forcing us to scrutinize more closely the vast array of attacks of all sorts which beset our patients, both those attacks that threaten his existence and those that are but nettles. In this field much remains to be clarified and the contribution of ordinary clinical observation has by no means been exhausted.

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Paralytic Poliomyelitis in Canada, 1960

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IT IS estimated that to June 1960 more than 32 million doses of killed poliovirus vaccine had been distributed in Canada and that about 70% of the Canadian population under 40 years of age had received three or more doses of vaccine. The quantity of vaccine released was sufficient to ensure that every child, woman and man under 40 received about 2.5 c.c. of vaccine. There were, however, appreciable differences in the acceptance rate in the provinces, ranging from an average of 1.7 per person in one province to 3.8 per person in another province.

The incidence of paralytic poliomyelitis in Canada in 1960 was the second highest registered since 1954. A total of 909 cases was reported to the Epidemiology Division, Department of National Health and Welfare, in 1960, an attack rate of 5.1 per 100,000 population. The number of deaths reported was 76, a case fatality rate of 8.4%.

The high incidence in 1960 was predictable after the 1959 epidemic year. Similar high incidence was experienced in 1954 following the 1953 epidemic.

The number of cases reported in the first six months of 1960 was the highest ever recorded for that period in Canada, being well above the figures for the epidemic years 1953 and 1959 (Fig. 1).

During July it appeared that the restraining, limiting and localizing effect of vaccination was beginning to be felt. The sharp seasonal rise experienced in previous high-incidence years did not materialize. Whereas, to the first week of July, the 1960 cumulative total was the highest ever recorded in Canada, by the first week of August the 1960 incidence was well below that registered in epidemic years.

The unexpected factor in 1960 was the emergence of the type III poliovirus. Previously in Canada type III was encountered only sporadically, but in 1960 it became the epidemic strain in many provinces, accounting for about 45% of the total virus isolations.

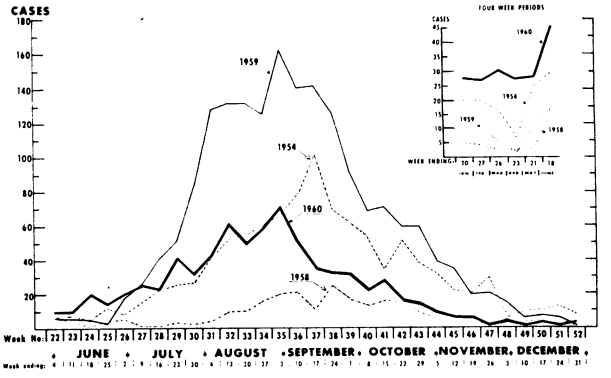

Fig. 1.—Paralytic poliomyelitis: reported weekly incidence, 1960 and specified years, Canada.

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